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# Aqueous      Metal-Catalyzed      Living      Radical Polymerization: Water-Assisted Highly Active Catalysis

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## ABSTRACT

A really catalytic aqueous living radical polymerization was achieved through ligand design for ruthenium-based catalyst. A phenolic phosphine ligand [PPh<sub>2</sub>(*p*PhOH)] was combined with a Cp\*-based tetramer ruthenium complex, and the formed complex showed a high catalytic activity for aqueous living radical polymerizations of hydrophilic methacrylates (e.g., PEGMA and HEMA) in conjunction with a chlorine initiator [H-(MMA)<sub>2</sub>-Cl]. The catalytic aqueous system allowed a very fast living polymerization, a block copolymerization and syntheses of high molecular weight polymers (DP<sub>n</sub> ~ 1000) with narrow MWDs. Importantly, the activity was enough high to control these polymerizations using just catalytic amount of the complex, although the polymerizations were performed at low temperature (40°C). Such an advanced catalysis would be caused not only by a simple hydrophilicity of the ligand but also by a water-assisted dynamic transformation from the original saturated form [Cp\*RuCl(PR<sub>3</sub>)<sub>2</sub>; 18e] into an unsaturated but active one [Cp\*RuCl(PR<sub>3</sub>); 16e] upon which water molecule(s) may additionally coordinate for further stabilization, as demonstrated by <sup>31</sup>P NMR analyses.

**Keywords:** living radical polymerization; aqueous polymerization; ruthenium; catalyst; block copolymerization; phosphine

**Running Head:** Aqueous Metal-Catalyzed Living Radical Polymerization

## Introduction

Biological reactions in nature are naturally performed in water with accurate control and selectivity. Therein reactants and reactive sites are recognized water-soluble substrates (or *vice versa*) via hydrogen-bonding, hydrophobic, and other weak interactions, by which rigorously selective reactions efficiently proceed under mild conditions. On the other hand, in general, our chemists are not good at conducting aqueous systems for some reaction control, because water is among the most “polar” compounds often involving side-reactions and deactivation of substrates, intermediates, and/or catalysts. This comparison indicates that one can achieve similar aqueous reaction by mimicking biological reactions, particularly by utilizing the weak interactions found in water.

In sharp contrast to ionic polymerizations and related polar organic reactions, radical polymerization is inherently “robust” against highly polar media and functionalities and thus generally immune to the “poisonous” effect of water, because radical species are electronically natural and thus tolerant of polar groups. It is therefore common in industrial polymer production to carry out radical polymerization in water or in aqueous media, typically in emulsion and dispersion processes. Though these processes are technically established, the precision control of polymer architecture and molecular weight is not possible.

Now that living radical polymerization has been achieved for a variety of monomers including functional derivatives,<sup>1-4</sup> the precision control of radical polymerization in water is of interest and significant not only for the use of functional and hydrophilic monomers but also from environmental viewpoints or for bioapplications. Particularly, “polymer bioconjugation”,<sup>5-7</sup> or covalently linking synthetic polymers to biopolymers, has attracted attention in pharmaceutical and fine material applications, and for this the realization of fine control in “aqueous” polymerization is obviously required, because most of biomolecules are soluble and active just in water to form meaningful structures for their functions.

Contemporary living radical polymerizations include those with transition metal-catalyst.<sup>1,8-14</sup>

Herein a metal catalyst catalyzes reversible activation of carbon–halogen bond ( $\sim\sim\sim\text{C}-\text{X} \leftrightarrow \sim\sim\sim\text{C}\cdot$ ;  $\text{X} = \text{halogen}$ ) of a carbon–halogen bond in an alkyl halide as initiator and/or in a dormant polymer terminal under one-electron redox catalysis ( $\text{Mt}^n \leftrightarrow \text{XMt}^{n+1}$ ;  $\text{Mt} = \text{transition metal such as Ru, Fe, Ni, and Cu}$ ), to generate a growth-active radical intermediate at a low concentration and thereby to suppress bimolecular termination and other side-reactions (**Scheme 1**). With high initiating efficiency and precise controllability, the metal-catalyzed systems are superior to other living radical polymerizations in the synthesis of well-defined architectures (e.g., block copolymers) and hybridization/conjugation with other (bio)molecules.

### Scheme 1

On the other hand, the metal catalysts are usually sensitive to polar functions that often induce unfavorable interactions, thus suffering from a limitation in applicable monomers and solvents and from the contamination of resultant polymers with their residues. It is thus increasingly important to develop transition-metal catalysts that are both robust against polar groups, soluble in water, and active enough to allow the extreme reduction of catalyst does. An ultimate goal, in turn, calls for the fine reaction control in *water* for hydrophilic monomers, a really “catalytic” amount of the catalyst, and ready removal of its residues from the products. To our knowledge, however, such a “real” aqueous catalysis is virtually unavailable thus far for living radical polymerization,<sup>15</sup> and most of aqueous systems require a relatively high dosage of a catalyst ( $[\text{catalyst}]_0/[\text{initiator}]_0 \sim 1$ ) for fine control.<sup>16-20</sup> This is likely due to the poor solubility of metal complexes in water and their high sensitivity to the interaction with water.

We have recently found that pentamethylcyclopentadienyl ( $\text{Cp}^*$ ) ruthenium complexes  $[\text{Cp}^*\text{Ru}(\text{Cl})\text{L}_2]$ ;  $\text{L} = \text{phosphine}$ ], in-situ prepared from a tetrameric precursor ( $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$ ), are active, robust, and universal catalysts for living radical polymerization in ethanol (**Scheme 2**).<sup>21</sup> The ligand/cocatalyst combination of tri-*m*-tolylphosphine  $[\text{P}(m\text{Tol})_3]$ ;  $m\text{Tol} = m\text{-MeC}_6\text{H}_4$ ] and a hydrophilic amine [2-dimethylamino-1-ethanol:  $\text{Me}_2\text{N}(\text{CH}_2)_2\text{OH}$ ] allowed fast living radical polymerizations and fine molecular weight control ( $M_w/M_n < 1.2$ ) for a variety of methacrylates. This catalysis is in fact

tolerant of polar groups to give well-defined homopolymers and random or block copolymers of functional monomers. It is proposed that an essential factor for the improved catalysis is the dynamic transformation of  $\text{Cp}^*\text{RuClP}(m\text{Tol})_3$  (a 16e unsaturated “active” complex) from  $\text{Cp}^*\text{RuCl}[\text{P}(m\text{Tol})_3]_2$  (an 18e starting pre-catalyst) in the alcoholic medium, which is supposed to promote the catalysis.

## Scheme 2

The high catalytic activity of the  $\text{Cp}^*\text{Ru}$  system in ethanol suggests a similarly active and efficient catalysis in water, where the solvent molecule may not only be non-interfering but also positively activates the catalyst. In fact, our preliminary results indicate the enhancement of the  $\text{RuCp}^*$  catalytic cycle by the addition of a small amount of water into ethanol solvent, and in-situ  $^{31}\text{P}$  NMR analysis showed the labile and dynamic coordination of the Ru center by the added water. These observations imply that, for these catalysts, water is not only a friendly solvent but an activator as well.

This work is to direct polymerization control from “in the presence of water” to “in pure water”. A ligation of 4-(hydroxyphenyl)diphenylphosphine [ $\text{PPh}_2(p\text{PhOH})$ ] on the  $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$  precursor permitted *aqueous* living radical polymerizations of hydrophilic methacrylates. The catalytic activity was very high to allow following features: a very fast living polymerization; a chain extension or block copolymerization via sequential and in-situ monomer addition; a reduction of catalyst concentration without any loss of controllability; the synthesis of high molecular weight polymers with narrow molecular weight distributions (MWDs); and, additionally, fine control of the polymerization of 2-hydroxyethyl methacrylate (HEMA) in water without forming insoluble product or gel.

## Experimental Section

**Materials.** Poly(ethylene glycol) methacrylate [PEGMA;  $\text{CH}_2=\text{CMeCO}_2(\text{CH}_2\text{CH}_2\text{O})_n\text{Me}$ ;  $\text{Me} = \text{CH}_3$ ;  $n = 8.5$  on average] (Aldrich) was purified by passing through an inhibitor removal column (Aldrich) and subsequently degassed by three-time vacuum-argon bubbling cycles before use. HEMA (Aldrich; >99 %) was distilled under reduced pressure before use. All the ligands and materials of ruthenium complexes were used as received without further purification and handled in a glovebox (M. Braun Labmaster 130) under a moisture- and oxygen-free argon atmosphere ( $\text{H}_2\text{O} < 1$  ppm;  $\text{O}_2 < 1$  ppm): Tri-*m*-tolylphosphine (Strem; >98 %), (4-hydroxyphenyl)diphenylphosphine (Aldrich; 98 %), tris(hydroxymethyl)phosphine (Strem; >85 %), tetrakis(hydroxymethyl)phosphonium chloride (Aldrich; 80 % solution in water), formaldehyde (Aldrich, 37 % solution in water), hexamethylenetetramine (Aldrich; >99.5 %), ruthenium(III) chloride hydrate (Wako; >99.9 %), 1,2,3,4,5-pentamethylcyclopentadiene (Strem; 98 %), lithium triethylhydridoborate (Aldrich; 1.0 M solution in THF). The hydrophilic phosphine ligand, 1,3,5-triaza-7-phosphaadamantane (PTA), was prepared according to the literature.<sup>22</sup> The tetramer precursor ruthenium complex  $[\text{RuCp}^*(\mu_3\text{-Cl})]_4$ <sup>23</sup> and the chlorine initiator  $[\text{H}-(\text{MMA})_2\text{-Cl}]$ <sup>24</sup> were also prepared according to the literature. Toluene (Kishida Kagaku; purity >99 %) was dried and purified by passing through purification columns (Solvent Dispensing System; Glass Contour) and bubbled with dry nitrogen for more than 15 min immediately before use. Ethanol (Wako; dehydrated; 99.5 %), water (Wako; distilled), and buffer solutions (TCI) were bubbled with dry nitrogen for more than 15 min immediately before use.

**Polymerization Procedures.** Polymerization was carried out by the syringe technique under dry argon in baked glass tubes equipped with a three-way stopcock or in sealed glass vials. A typical procedure for the polymerization of PEGMA with  $\text{H}-(\text{MMA})_2\text{-Cl}/[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4/\text{PPh}_2(p\text{PhOH})$  is given. In a 50-mL round-bottom flask was placed  $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})]_4$  (4.3 mg, 0.008 mmol),  $\text{PPh}_2(p\text{PhOH})$  (9.7 mg, 0.032 mmol), toluene (4 mL), and ethanol (1 mL). The solution was stirred at 60 °C until the color changed from black-brown to red-brown (30 minutes stirring). After cooling the flask

to room temperature, the solution was evaporated and dried 2 hours at room temperature. After filling dry argon to the flask, PEGMA (1.76 mL, 4.0 mM), buffer solution (6.15 mL), and a solution of H-(MMA)<sub>2</sub>-Cl (0.091 mL, 437.4 mM in ethanol, 0.40 mmol) were sequentially added under dry argon at 0 °C, where the total volume of the reaction mixture was thus 8.0 mL. Immediately after mixing, aliquots (0.50 mL–1.0 mL each) of the solution were injected into glass tubes that were then sealed (except when a stopcock was used) and placed in an oil bath kept at desired temperature. In predetermined intervals, the polymerization was terminated by cooling the reaction mixtures to –78 °C. Monomer conversion was directly determined from the <sup>1</sup>H NMR spectrum of the solution aliquot. The quenched reaction solutions were evaporated to dryness to give the products that were subsequently dried overnight under vacuum at room temperature.

**Measurements.**  $M_n$  and  $M_w/M_n$  of the polymers were measured by size-exclusion chromatography (SEC) at 40 °C in DMF containing 10 mM LiBr as an eluent on three polystyrene-gel columns [Shodex KF-805L (pore size: 20–1000 Å; 8.0 mm i.d. × 30 cm); flow rate, 1.0 mL/min] connected to a Jasco PU-2080 precision pump, a Jasco RI-2031 refractive-index detector, and a Jasco UV-2075 ultraviolet detector. The columns were calibrated against 13 standard poly(MMA) samples (Polymer Laboratories;  $M_n = 630$ –1,200,000,  $M_w/M_n = 1.06$ –1.22) as well as the monomer. <sup>1</sup>H NMR and <sup>31</sup>P NMR spectra were measured at room temperature on a JEOL JNM-LA500 spectrometer operating at 500.16 and 202.47 MHz, respectively. For the <sup>31</sup>P NMR analyses, a capillary of (C<sub>2</sub>H<sub>5</sub>O)<sub>2</sub>POH solution (50 mM in toluene-*d*<sub>8</sub>) was used to adjust the chemical shift (12 ppm for the phosphite).



## Result and Discussion

### 1. Effects of Water on Polymerization of PEGMA

We have recently presented that the ethanol-mediated catalytic system with  $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4/\text{P}(m\text{Tol})_3]$  in conjunction with an amino alcohol (cocatalyst) was active enough to control radical polymerization with a variety of functional methacrylates at 40°C.<sup>21</sup> We first added water into the ethanol-mediated system to examine effects of water on the catalysis. Polymerizations of PEGMA was then performed with  $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4/\text{P}(m\text{Tol})_3]$ , coupled with  $[\text{H}-(\text{MMA})_2\text{-Cl}]$  as an initiator in mixed solvent of ethanol (EtOH) and water at 40 °C:  $[\text{PEGMA}]_0/[\text{H}-(\text{MMA})_2\text{-Cl}]_0/[[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]_0/[\text{P}(m\text{Tol})_3]_0 = 500/5.0/0.5/4.0$  mM (100 mer condition). In these particular runs, no cocatalyst was employed, so that the effects of water could be clarified without being superimposed with other factors. In pure and dry ethanol, the polymerization was fairly controlled to give polymers of narrow MWDs ( $M_w/M_n < 1.12$ ), but was rather slow (144 h for 90 % conversion). As water was added into the alcoholic solvent, the reactions were apparently accelerated. Especially, with 25-vol% water, a very fast polymerization proceeded (8 h for 96 % conversion), nevertheless the MWDs were controlled as in pure ethanol system ( $M_w/M_n < 1.12$ ). When water content was increased to 50 vol%, a faster but less controlled polymerization occurred ( $M_w/M_n \sim 1.3$ ), as the system became heterogeneous due to poor solubility of the ruthenium catalyst in the water-rich medium. Thus, water addition within a certain range (<50 vol% relative to ethanol) was found to be effective for acceleration, or the effective promotion of the catalytic cycle, without a loss of the controllability and system homogeneity.

**Figure 1**

### 2. Effects of Water on Ruthenium Complexes

Whenever a coordinatively saturated complex [e.g.,  $\text{Cp}^*\text{RuCl}(\text{PR}_3)_2$ ;  $\text{PR}_3$  = phosphine] is employed as a catalyst for the redox-mediated living radical polymerization, it should be transformed

into a certain coordinatively unsaturated form [e.g.,  $\text{Cp}^*\text{RuCl}(\text{PR}_3)$ ] so as to catalyze initiation and propagation. Thus, we examined the coordination behavior of the  $\text{Cp}^*\text{Ru}$  complex in the presence of water to clarify the reason why it accelerates the polymerization.

The tetramer precursor,  $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]_4$ , was heated with the ligand  $[\text{P}(m\text{Tol})_3]$  in toluene to form the bisphosphine complex,  $\text{Cp}^*\text{RuCl}[\text{P}(m\text{Tol})_3]_2$ . Toluene was evaporated and the complex was aged in an EtOH/water mixed solvent (60/40, v/v) at 40 °C for 2 h, before evaporated and re-dissolved in EtOH- $d_6$  for  $^{31}\text{P}$  NMR analysis. Aging in water-free pure EtOH was also examined for comparison. Figure 2 shows the  $^{31}\text{P}$  NMR spectra of the phosphine ligand (A) and the ruthenium complexes after aging in pure EtOH (B) and in EtOH/water mixture (C). For the complex after aging in EtOH (Figure 2B), two small peaks were detected at 43.7 and 0.2 ppm, in addition to the main signal (45.3 ppm) from the bisphosphine form. The small peak at 0.2 ppm is at the same position as with the free phosphine (Figure 2A), indicating that a part of phosphines on the originally bis-ligated complex is liberated. The other minor peak at 43.7 ppm is therefore most likely indicative of a mono-ligated complex  $\text{Cp}^*\text{RuCl}[\text{P}(m\text{Tol})_3]$ .

On the other hand, the 45.3-ppm peak for the bis-ligated complex was completely absent with the sample aged in the EtOH/water mixture (Figure 2C), and a new peak was instead observed at a higher field (42.9 ppm), while the free signal (0 ppm) was relatively intense. Therefore, the new peak is probably from another complex carrying only one phosphine ligand. Because this peak is slightly but obviously different in chemical shift from the corresponding higher-field peak for the ethanol-aged sample (43.7 vs 42.9 ppm), water molecule(s) in the “wet” ethanol might dynamically coordinate the vacant site of the mono-ligated unsaturated complex ( $\text{Cp}^*\text{RuCl}[\text{P}(m\text{Tol})_3]$ ) for additional stabilization (Scheme 3). The labile ligation of water would facilitate the incipient generation of the unsaturated form, which is active in radical formation and thereby leads to the acceleration of polymerization in the presence of water.

**Figure 2**

### Scheme 3

### 3. Aqueous Living Radical Polymerization through Ligand Design

Water addition was found to the promotion of catalytic cycle in the metal-catalyzed living radical polymerization with  $\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4/\text{P}(m\text{Tol})_3$ . However, the hydrophobicity of  $\text{P}(m\text{Tol})_3$  incurred poorer polymerization control in the presence of an excessively large amount of water (>50 vol% relative to EtOH) due to the poor solubility. Thus, our next efforts were directed to the search of more hydrophilic phosphines that would give a fast and efficient but controlled catalysis in water.

Three hydrophilic phosphine ligands were then employed for the ruthenium tetramer precursor ( $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$ ) in the aqueous polymerizations of PEGMA (Figure 3): (4-hydroxyphenyl)diphenylphosphine [ $\text{PPh}_2(p\text{PhOH})$ ]; 1,3,5-triaza-7-phosphaadamantane (PTA); and tris(hydroxymethyl)phosphine (THMP). For in-situ ligation an 8-fold molar excess of these phosphines were mixed with  $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$  in toluene or the mixed solvent with ethanol.<sup>25</sup> After aging for 2 hr the solution was evaporated, the as-obtained complex obtained complex was directly employed for the polymerization in aqueous buffer solution ( $\text{H}_3\text{BO}_3\text{-KCl-NaOH}$ ) at pH 8, where the concentrations of components were adjusted to  $[\text{PEGMA}]_0/[\text{H-(MMA)}_2\text{-Cl}]_0/[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]_0/[\text{ligand}]_0 = 500/5.0/0.5/4.0$  mM (the so-called the 100 mer condition). In contrast to that with  $[\text{P}(m\text{Tol})_3]$ , the polymerization solutions were almost homogeneous with the three phosphines.

Among the three ligands, only the aromatic phosphine,  $\text{PPh}_2(p\text{PhOH})$ , induced a fast and controlled polymerization (97-% conversion in 2 h): GPC curves shifted to higher molecular weight with conversion, while keeping narrow MWDs ( $M_w/M_n < 1.40$ ). On the other hand, the polymerizations with aliphatic PTA or THMP were not controlled and gave much higher polymers of broader MWDs.

Figure 3

### 4. Evidence for Living Polymerization in Water

To examine the “living” nature of the polymerization with  $\text{PPh}_2(p\text{PhOH})$ , a monomer-addition experiment was performed (Figure 4). PEGMA was first polymerized in water (pH 8 buffer) with  $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]/\text{PPh}_2(p\text{PhOH})$ , in conjunction with  $\text{H}-(\text{MMA})_2\text{-Cl}$  as an initiator:  $[\text{PEGMA}]_0/[\text{H}-(\text{MMA})_2\text{-Cl}]_0/[[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]_0]/[\text{ligand}]_0 = 500/20/0.5/4.0$  mM; 25 mer condition. When the monomer conversion reached 86-% conversion (45 min), a fresh feed of PEGMA was added to the reaction mixture. A smooth and near quantitative polymerization ensured (96+ % in an additional 3 h), and the linear  $M_n$ -conversion plots and the narrow MWDs ( $M_w/M_n \sim 1.15$ ) demonstrated a living polymerization.

**Figure 4**

In this aqueous living radical polymerization, molecular weight could also be controlled by changing the  $[\text{monomer}]_0/[\text{initiator}]_0$  feed ratio. Figure 5 shows SEC profiles of polymers obtained at 25, 100, 500, and 1000 of the ratio.<sup>26</sup> Under all these conditions, molecular weights were fairly controlled and increased according to the feed ratio.<sup>27</sup> Note that advanced catalysis (i.e., combination of fast polymerization, complete monomer consumption, and narrow MWDs) was retained for a high  $[\text{monomer}]_0/[\text{initiator}]_0$  ratio (= 1000) and without any cocatalyst.

**Figure 5**

## 5. Reduction of Catalyst Dose

The enhanced catalytic activity of the  $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]/\text{PPh}_2(p\text{PhOH})$  system in water encouraged us to reduce the catalyst amount, because metal residue in products is unfavorable, especially in some bioapplications. For example, the complex concentration was reduced from 2.0 mM in the standard system (Figures 4 and 5) to 1.0, 0.40, and 0.20 mM in the 25-mer synthesis at  $[\text{PEGMA}]_0/[\text{H}-(\text{MMA})_2\text{-Cl}]_0 = 500/25$  mM (Figure 6). The polymerization decelerated with less catalyst, as expected, but the catalytic activity was high enough to reach near complete monomer

consumption within several hours. Polymer molecular weight increased with conversion, while narrow MWDs maintained, although the lowest catalyst dose (0.2 mM) in fact resulted in broader distributions. A catalyst load as low as 0.4 mM was enough to catalyze living radical polymerization ( $M_w/M_n = 1.29$  at 94 % conversion), and in this particular case the as-obtained polymer solution was almost colorless. Under these conditions, the initial catalyst dose is 1/50 to initiator by mole and 170 ppm to monomer by weight, indicating a much higher catalytic activity relative to previously known aqueous systems with ruthenium catalysts.

**Figure 6**

## 6. Aqueous Polymerization of HEMA and MANa

The  $[\text{RuCp}^*(\mu_3\text{-Cl})]_4/\text{PPh}_2(p\text{PhOH})$  system was applicable for other hydrophilic monomers such as 2-hydroxyethyl methacrylate (HEMA). It has been considered difficult to synthesize linear poly(HEMA) via radical polymerization in water, where crosslinking via the transesterification among the pendent hydroxyl groups are often unfavourable.<sup>28</sup> This rendered previous controlled radical polymerizations of HEMA available only in alcohol or mixed solvents with water.<sup>29,30</sup> In contrast, the catalytic system with  $\text{PPh}_2(p\text{PhOH})$  allowed a controlled aqueous polymerization of HEMA at 40 °C in water (buffered; pH 8.0):  $[\text{HEMA}]_0/[\text{H}-(\text{MMA})_2\text{-Cl}]_0/[\text{RuCp}^*(\mu_3\text{-Cl})]_4/[\text{PPh}_2(p\text{PhOH})]_0 = 2000/40/0.5/4.0$  mM (Figure 7). The polymerization smoothly proceeded without insoluble or crosslinked products, and the polymers showed narrow MWDs (reaching  $M_w/M_n = 1.28$  at higher conversion). The  $M_n$  was controlled in accordance with the monomer to initiator feed ratio. To our knowledge, this is the first report of the aqueous polymerization control for HEMA.<sup>31</sup>

**Figure 7**

Polymerization of sodium methacrylate (NaMA) was also studied with the same aqueous catalytic system (Supplement Information, Figure S1). Even with the hydrophilic ligand, the ruthenium

complex was insoluble in water containing NaMA, and thus 25 vol% of EtOH was added to make homogeneous solutions. Monomer conversion reached 82 % in 72 h, at which stage, however, a part of polymeric product began to precipitate. SEC analysis showed that the polymerization was somewhat controlled: polymer molecular weight increased with conversion, though a small additional peak was observed in the lower molecular weight region. Further investigations are proceeding for NaMA polymerization.

## 7. Block and Random Copolymerizations

With precision control achieved for homopolymerization in water with a catalytic amount of the ruthenium complex, it was then applied for block and random copolymerizations to demonstrate its utility. When the aqueous living radical polymerization of PEGMA was almost finished (94 % conversion, 1.5 h), neat HEMA was added (50 eq to initiator):  $[\text{PEGMA}]_0/[\text{H}-(\text{MMA})_2-\text{Cl}]_0/[[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]_0]/[\text{ligand}]_0/[\text{HEMA}]_{\text{add}} = 500/20/0.5/4.0/1000 \text{ mM}$  (Figure 8). The second monomer was smoothly consumed to 80 % in 10 h. The SEC curves before and after the HEMA addition showed a clear peak shift without any shoulder or tailing. The poly(PEGMA) chains in the first stage thus almost quantitatively grew with HEMA, free from side reactions, to give block copolymers. Living random copolymerization of PEGMA and HEMA was also possible (Supplementary Information, Figure S2).

**Figure 8**

## 8. Effects of pH on Polymerization Control

For some aqueous reactions and polymerizations, pH adjustment is essential for precision control. In the ruthenium-catalyzed aqueous living radical polymerizations (see above), a pH 8.0 buffer with  $\text{H}_3\text{BO}_3$ , KCl, and NaOH was employed as the solvent. Other buffer solutions were also employed for PEGMA:  $\text{KH}_2\text{PO}_4/\text{NaOH}$ , pH 6.0;  $\text{H}_3\text{BO}_3/\text{KCl}/\text{NaOH}$ , pH 9.6. Fast and quantitative

polymerizations proceeded with these solutions, however, the obtained polymers were less controlled ( $M_w/M_n > 1.6$ ) (Supplementary Information, Figure S3). As the ligand is phenolic, the solubility of the complex or the phosphine's coordination would be sensitive to pH: a poor solubility of the catalyst at lower pH; an unfavorable reaction of the phenoxy anion ( $\text{ArO}^-$ ) with  $\text{Ru-Cl}$  to form  $\text{Ru-OAr}$  at higher pH. Further ligand design is being proceeding in our group to achieve aqueous living polymerization in a wide range of pH.

## Conclusion

This work has achieved aqueous living radical polymerizations of PEGMA and HEMA via the ligand design of ruthenium complex. The ruthenium complex, in-situ prepared from  $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$  and  $\text{PPh}_2(p\text{PhOH})$ , led to a fast and complete living radical polymerization in water at a relatively low temperature (40 °C) and with a low ruthenium dose (1/50 to initiator; 170 ppm to monomer), to give PEGMA–HEMA block copolymers and high polymers ( $\text{DP} > 1000$ ) with narrow MWDs. Such an advanced catalytic control is realized not only by a simple hydrophilicity of the ligand but by a water-promoted catalytic cycle (as seen by  $^{31}\text{P}$  NMR). Water likely induces a catalyst transformation via the ligand elimination, from the original saturated form  $[\text{Cp}^*\text{RuCl}(\text{PR}_3)_2; 18\text{e}]$  into an unsaturated but active form  $[\text{Cp}^*\text{RuCl}(\text{PR}_3); 16\text{e}]$  upon which water molecule(s) may additionally coordinate for further stabilization. This system would open the door to bioconjugation and other applications that need living polymerizations in water.

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## Caption for Figures and Schemes

### Scheme 1. Metal-Catalyzed Living Radical Polymerization

### Scheme 2. Cp\*-based Ruthenium Catalyst for Ethanol-Mediated Living Radical Polymerization

### Scheme 3. Proposed Transformation of Cp\*RuCl[P(*m*Tol)<sub>3</sub>]<sub>2</sub> via Aging in EtOH/H<sub>2</sub>O at 40 °C

**Figure 1.** Effects of water on the polymerization of PEGMA with Cp\*RuCl[P(*m*Tol)<sub>3</sub>]<sub>2</sub> in conjunction with H-(MMA)<sub>2</sub>-Cl in EtOH/H<sub>2</sub>O at 40 °C: [PEGMA]<sub>0</sub> = 0.5 M; [H-(MMA)<sub>2</sub>-Cl]<sub>0</sub> = 5.0 mM; [Cp\*RuCl[P(*m*Tol)<sub>3</sub>]<sub>2</sub>]<sub>0</sub> = 2.0 mM. EtOH/H<sub>2</sub>O (v/v %) = 100/0 (■); 95/5 (▼); 75/25 (●); 50/50 (▲). The ruthenium complex was prepared via mixing of [Cp\*Ru(μ<sub>3</sub>-Cl)]<sub>4</sub> and P(*m*Tol)<sub>3</sub> in toluene at 60 °C for 12 hours, followed by the evaporation for polymerization: [[Cp\*Ru(μ<sub>3</sub>-Cl)]<sub>4</sub>] = 0.5 mM; [P(*m*Tol)<sub>3</sub>] = 4.0 mM.

**Figure 2.** <sup>31</sup>P NMR (EtOH-*d*<sub>6</sub>, r.t.) analyses of Cp\*RuCl[P(*m*Tol)<sub>3</sub>]<sub>2</sub> for an investigation of water effects on the coordination. (A) P(*m*Tol)<sub>3</sub>; (B) Cp\*RuCl[P(*m*Tol)<sub>3</sub>]<sub>2</sub> after aging in EtOH; (C) Cp\*RuCl[P(*m*Tol)<sub>3</sub>]<sub>2</sub> after aging in EtOH/H<sub>2</sub>O (60/40 v/v%). The ruthenium complex was prepared via mixing of [Cp\*Ru(μ<sub>3</sub>-Cl)]<sub>4</sub> and P(*m*Tol)<sub>3</sub> in toluene at 60 °C for 12 h, followed by the evaporation for the aging experiment in EtOH or EtOH/H<sub>2</sub>O. The sample concentration for the <sup>31</sup>P NMR analyses: [P(*m*Tol)<sub>3</sub>] = 4.0 mM (A); [Cp\*RuCl[P(*m*Tol)<sub>3</sub>]<sub>2</sub>] = 4.0 mM (B, C).



**Figure 3.** Effects of phosphine ligand on an aqueous polymerization of PEGMA with  $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$  in conjunction with  $\text{H}-(\text{MMA})_2\text{-Cl}$  in  $\text{H}_2\text{O}$  (pH 8.0) at  $40^\circ\text{C}$ :  $[\text{PEGMA}]_0 = 0.5 \text{ M}$ ;  $[\text{H}-(\text{MMA})_2\text{-Cl}]_0 = 5.0 \text{ mM}$ ;  $[\text{ruthenium complex}]_0 = 2.0 \text{ mM}$ . The ruthenium complexes were prepared before the polymerization via mixing of  $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$  with phosphine ligand in solution at  $60^\circ\text{C}$ :  $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4] = 0.5 \text{ mM}$ ;  $[\text{phosphine}] = 4.0 \text{ mM}$ . The solvent and the aging time were changed according to the ligand: toluene, 12 h [PTA and  $\text{P}(m\text{Tol})_3$ ]; toluene/EtOH, 30 min [ $\text{PPh}_2(p\text{PhOH})$ ]; EtOH, 12 h (THMP). Phosphine: PTA ( $\blacktriangle$ );  $\text{PPh}_2(p\text{PhOH})$  ( $\bullet$ ); THMP ( $\blacktriangledown$ );  $\text{P}(m\text{Tol})_3$  ( $\blacksquare$ ).

**Figure 4.** Monomer-addition experiment of the aqueous living radical polymerization of PEGMA with  $\text{H}-(\text{MMA})_2\text{-Cl}/[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]/\text{PPh}_2(p\text{PhOH})$  in  $\text{H}_2\text{O}$  (pH 8.0) at  $40^\circ\text{C}$ :  $[\text{PEGMA}]_0 = 500 \text{ mM}$ ;  $[\text{H}-(\text{MMA})_2\text{-Cl}]_0 = 20 \text{ mM}$ ;  $[[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]]_0 = 0.5 \text{ mM}$ ;  $[\text{PPh}_2(p\text{PhOH})]_0 = 4.0 \text{ mM}$ ;  $[\text{PEGMA}]_{\text{add}} = 500 \text{ mM}$ . The ruthenium complex was prepared before the polymerization via mixing of  $[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]$  with  $\text{PPh}_2(p\text{PhOH})$  in toluene/EtOH at  $60^\circ\text{C}$  for 30 min, and directly employed for the polymerization via the evaporation.

**Figure 5.** Molecular weight control by the ratio of monomer to initiator ( $[\text{PEGMA}]_0/[\text{H}-(\text{MMA})_2\text{-Cl}]_0$ ) in the aqueous living radical polymerization of PEGMA with  $\text{H}-(\text{MMA})_2\text{-Cl}/[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]/\text{PPh}_2(p\text{PhOH})$  in  $\text{H}_2\text{O}$  (pH 8.0) at  $40^\circ\text{C}$ .  $[\text{PEGMA}]_0/[\text{H}-(\text{MMA})_2\text{-Cl}]_0/[[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]]_0/[\text{PPh}_2(p\text{PhOH})]_0 = 500/20/0.5/4.0$  (25 mer);  $500/5.0/0.5/4.0$  (100 mer);  $300/0.6/0.05/0.4 \text{ mM}$  (500 mer);  $300/0.3/0.05/0.4$  (1000mer). See Figure 4 for preparation of the ruthenium complex.

**Figure 6.** Reduction of catalyst dose in the aqueous living radical polymerization of PEGMA with  $\text{H}-(\text{MMA})_2\text{-Cl}/[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]/\text{PPh}_2(p\text{PhOH})$  in  $\text{H}_2\text{O}$  (pH 8.0) at  $40^\circ\text{C}$ .  $[\text{PEGMA}]_0 = 500 \text{ mM}$ ;  $[\text{H}-(\text{MMA})_2\text{-Cl}]_0 = 20 \text{ mM}$ ;  $[[\text{Cp}^*\text{Ru}(\mu_3\text{-Cl})_4]]_0 = 0.5, 0.25, \text{ or } 0.1 \text{ mM}$ ;  $[\text{PPh}_2(p\text{PhOH})]_0 = 4.0, 2.0, \text{ or } 0.8$

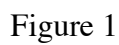
mM. Catalyst Concentration: 2.0 mM (●); 1.0 mM (▲); 0.4 mM (■). See Figure 4 for preparation of the ruthenium complex.

**Figure 7.** Aqueous polymerization of HEMA with H-(MMA)<sub>2</sub>-Cl/[Cp\*Ru(μ<sub>3</sub>-Cl)]<sub>4</sub>/PPh<sub>2</sub>(*p*PhOH) in H<sub>2</sub>O (pH 8.0) at 40 °C. [HEMA]<sub>0</sub> = 2.0 M; [H-(MMA)<sub>2</sub>-Cl]<sub>0</sub> = 40 mM; [[Cp\*Ru(μ<sub>3</sub>-Cl)]<sub>4</sub>]<sub>0</sub> = 0.5 mM; [PPh<sub>2</sub>(*p*PhOH)]<sub>0</sub> = 4.0 mM. See Figure 4 for preparation of the ruthenium complex.

**Figure 8.** Block Copolymerization of PEGMA and HEMA with H-(MMA)<sub>2</sub>-Cl/[Cp\*Ru(μ<sub>3</sub>-Cl)]<sub>4</sub>/PPh<sub>2</sub>(*p*PhOH) in H<sub>2</sub>O (pH 8.0) at 40 °C. [PEGMA]<sub>0</sub> = 0.5 M; [H-(MMA)<sub>2</sub>-Cl]<sub>0</sub> = 20 mM; [[Cp\*Ru(μ<sub>3</sub>-Cl)]<sub>4</sub>]<sub>0</sub> = 0.5 mM; [PPh<sub>2</sub>(*p*PhOH)]<sub>0</sub> = 4.0 mM; [HEMA]<sub>add</sub> = 1.0 M. See Figure 4 for preparation of the ruthenium complex.

## References

- (1) Ouchi, M., Terashima, T. & Sawamoto, M. *Chem Rev* **2009**, *109*, 4963-5050.
- (2) Hawker, C. J., Bosman, A. W. & Harth, E. *Chem Rev* **2001**, *101*, 3661-3688.
- (3) Moad, G., Rizzardo, E. & Thang, S. H. *Polymer* **2008**, *49*, 1079-1131.
- (4) Yamago, S. *Chem Rev* **2009**, *109*, 5051-5068.
- (5) Heredia, K. L. & Maynard, H. D. *Org Biomol Chem* **2007**, *5*, 45-53.
- (6) Nicolas, J., Mantovani, G. & Haddleton, D. M. *Macromol Rapid Comm* **2007**, *28*, 1083-1111.
- (7) Gauthier, M. A. & Klok, H. A. *Chem Commun* **2008**, 2591-2611.
- (8) Kamigaito, M., Ando, T. & Sawamoto, M. *Chem Rev* **2001**, *101*, 3689-3745.
- (9) Kamigaito, M., Ando, T. & Sawamoto, M. *Chem Rec* **2004**, *4*, 159-175.
- (10) Kamigaito, M. *Polymer Journal* **2010**.
- (11) Ouchi, M., Terashima, T. & Sawamoto, M. *Accounts Chem Res* **2008**, *41*, 1120-1132.
- (12) Matyjaszewski, K. & Xia, J. H. *Chem Rev* **2001**, *101*, 2921-2990.
- (13) Tsarevsky, N. V. & Matyjaszewski, K. *Chem Rev* **2007**, *107*, 2270-2299.
- (14) Rosen, B. M. & Percec, V. *Chem Rev* **2009**, *109*, 5069-5119.
- (15) Oh, J. K., Perineau, F., Charleux, B. & Matyjaszewski, K. *J Polym Sci Pol Chem* **2009**, *47*, 1771-1781.
- (16) Coca, S., Jasieczek, C. B., Beers, K. L. & Matyjaszewski, K. *J Polym Sci Pol Chem* **1998**, *36*, 1417-1424.
- (17) Ashford, E. J., Naldi, V., O'Dell, R., Billingham, N. C. & Armes, S. P. *Chem Commun* **1999**, 1285-1286.
- (18) Wang, X. S., Jackson, R. A. & Armes, S. P. *Macromolecules* **2000**, *33*, 255-257.
- (19) Wang, X. S. & Armes, S. P. *Macromolecules* **2000**, *33*, 6640-6647.
- (20) Lobb, E. J., Ma, I., Billingham, N. C., Armes, S. P. & Lewis, A. L. *J Am Chem Soc* **2001**, *123*, 7913-7914.
- (21) Yoda, H., Nakatani, K., Terashima, T., Ouchi, M. & Sawamoto, M. *Macromolecules* **2010**, *43*, 5595-5601.
- (22) Daigle, D. J., Pepperma, A. B. & Vail, S. L. *J Heterocyclic Chem* **1974**, *11*, 407-408.
- (23) Fagan, P. J., Ward, M. D. & Calabrese, J. C. *J Am Chem Soc* **1989**, *111*, 1698-1719.
- (24) Ando, T., Kamigaito, M. & Sawamoto, M. *Macromolecules* **1998**, *31*, 6708-6711.
- (25) According to the ligand, the solvent and the aging time were changed to accomplish the coordination or to improve solubility of the formed complex.
- (26) A condition with the 25 and 100 ratio is same as for study of the ligand effect (Figure 3) and that of the reduction of catalyst does (Figure 6), respectively.
- (27) Since the SEC molecular weights are calibrated with PMMA standards, the observed molecular weights cannot be compared with the calculated values based on the monomer/initiator feed ratio.
- (28) Robinson, K. L., Khan, M. A., Banez, M. V. D., Wang, X. S. & Armes, S. P. *Macromolecules* **2001**, *34*, 3155-3158.
- (29) Beers, K. L., Boo, S., Gaynor, S. G. & Matyjaszewski, K. *Macromolecules* **1999**, *32*, 5772-5776.
- (30) Fuji, Y., Watanabe, K., Baek, K. Y., Ando, T., Kamigaito, M. & Sawamoto, M. *J Polym Sci Pol Chem* **2002**, *40*, 2055-2065.
- (31) It is not clear if the control over radical propagation is related to the homogeneous polymerization without forming gel. The use of buffer pH 8 might contribute to it. This is now under investigation.



(A)  $P(mTol)_3$

(B)  $Cp^*RuCl(P(mTol)_3)_2$

After Aging in **EtOH** at 40°C

(C)  $Cp^*RuCl(P(mTol)_3)_2$

After Aging in **EtOH/H<sub>2</sub>O** at 40°C

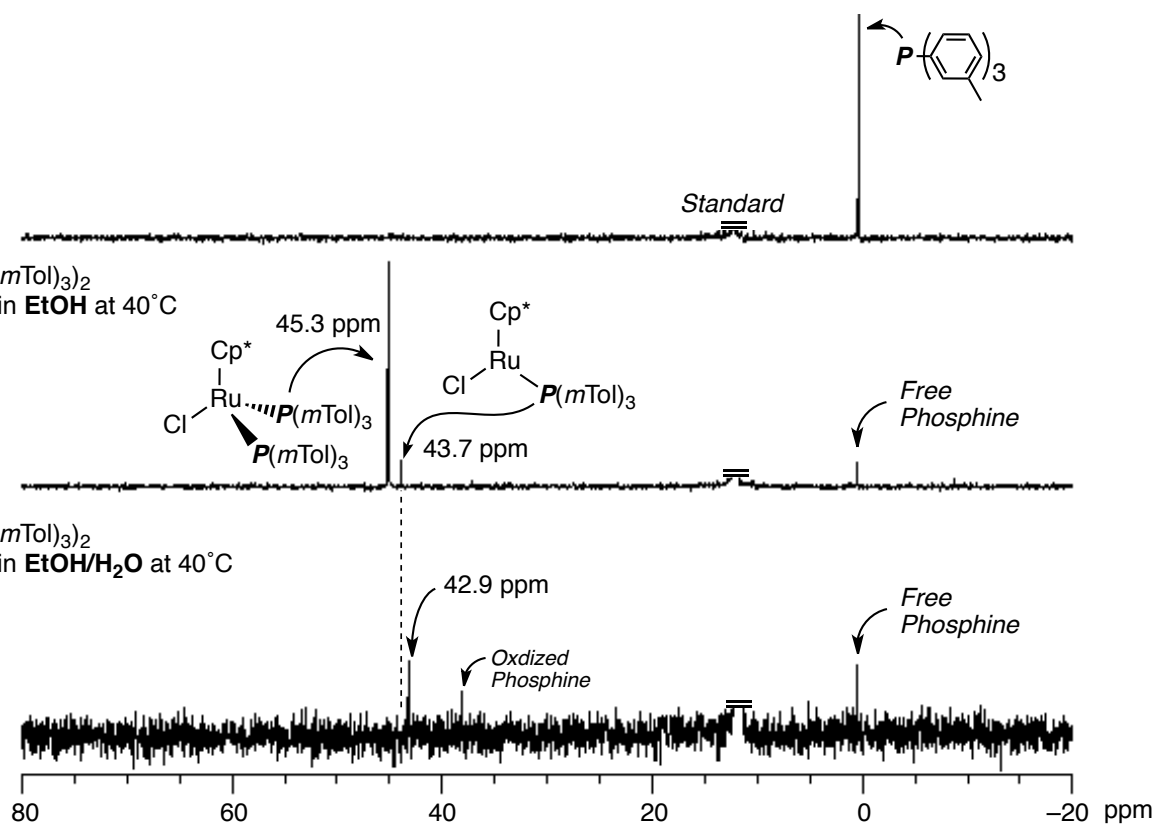


Figure 2

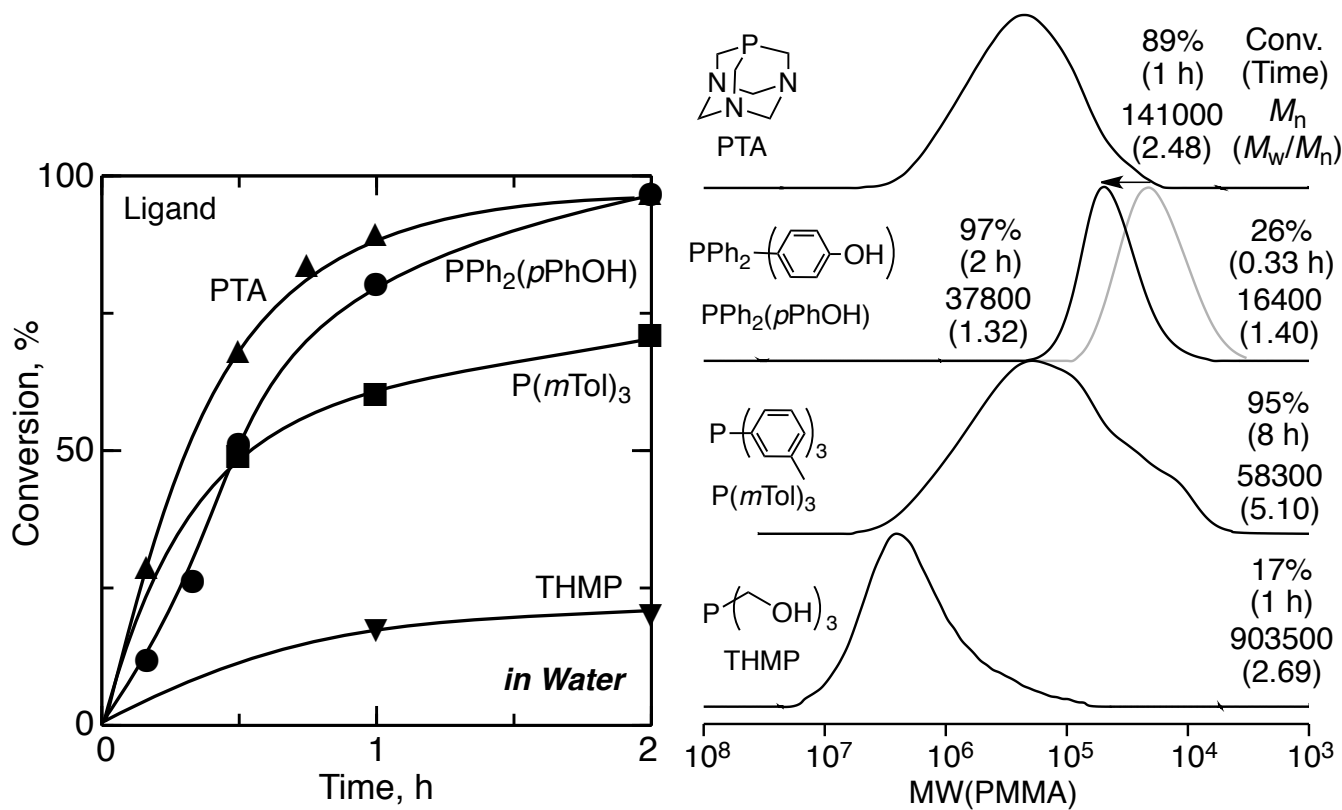


Figure 3

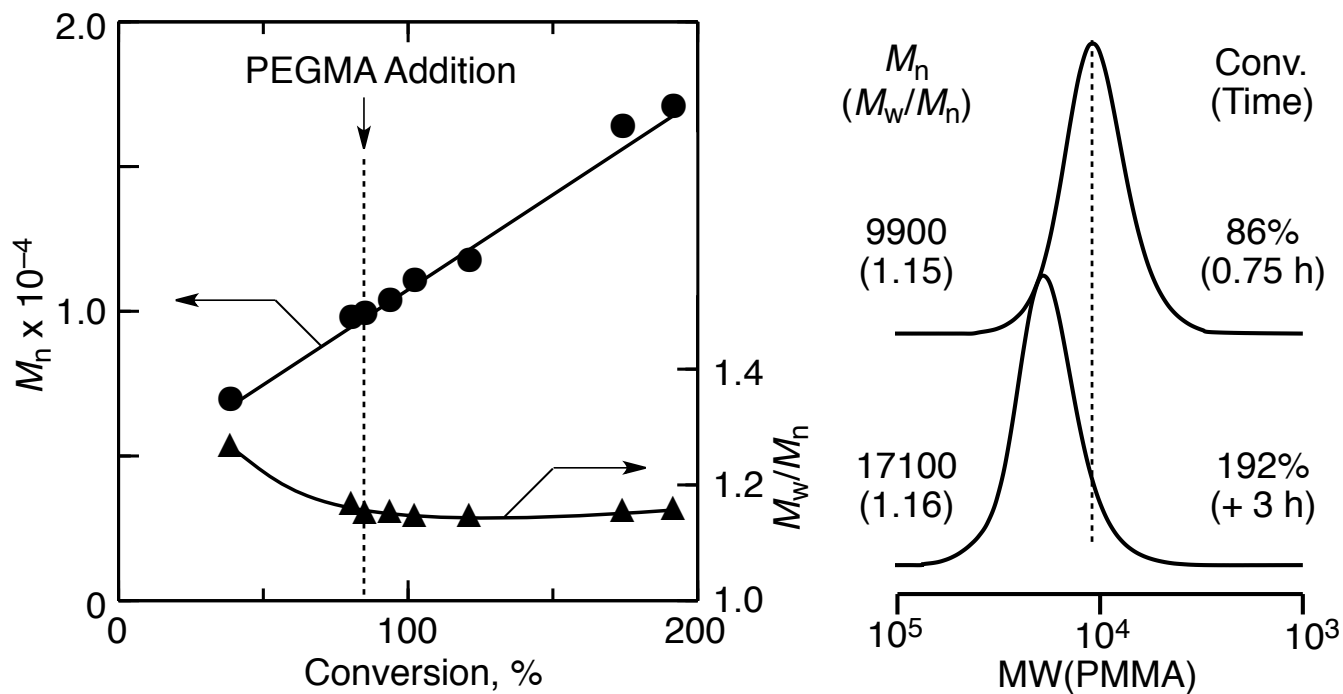


Figure 4

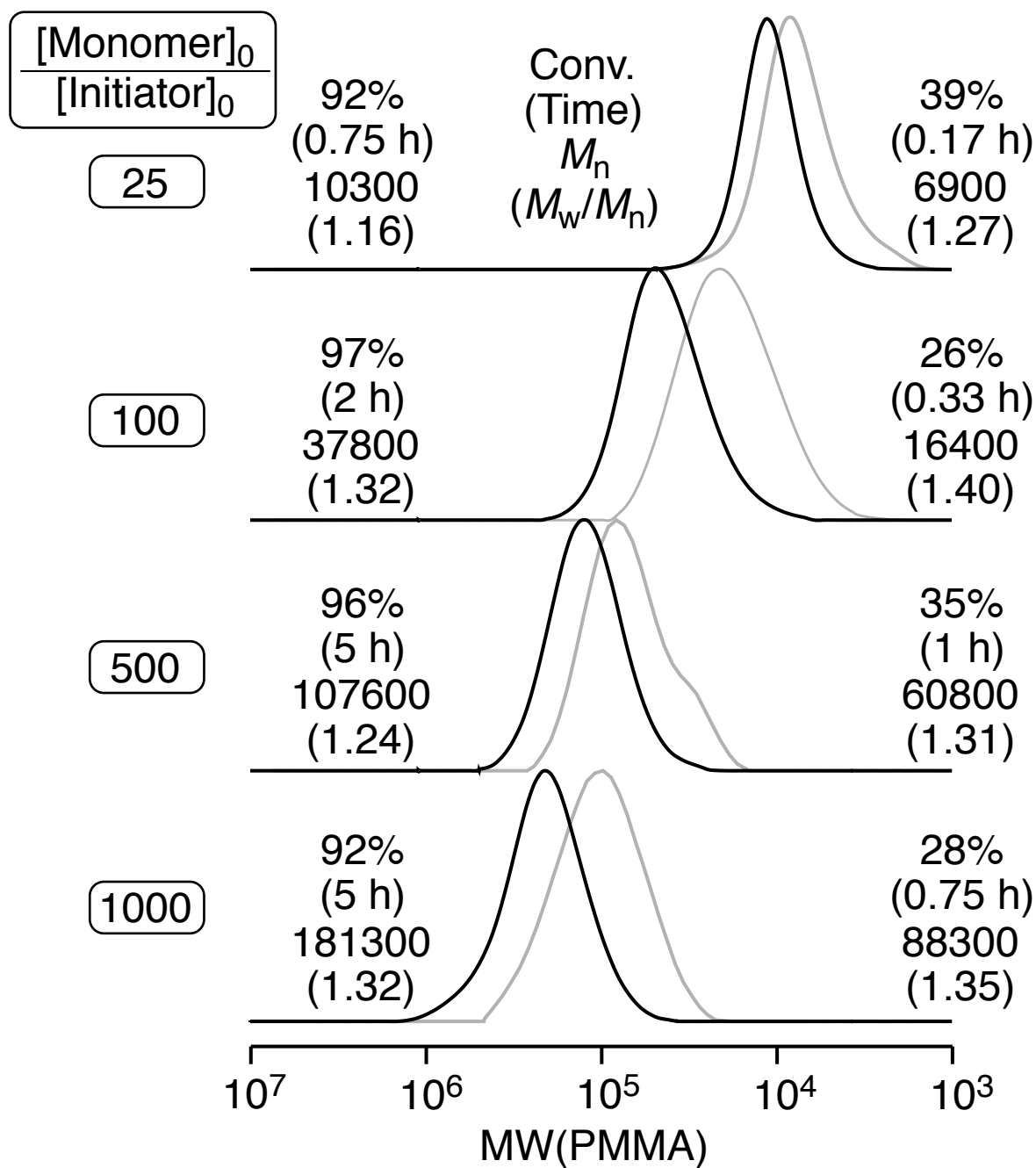


Figure 5

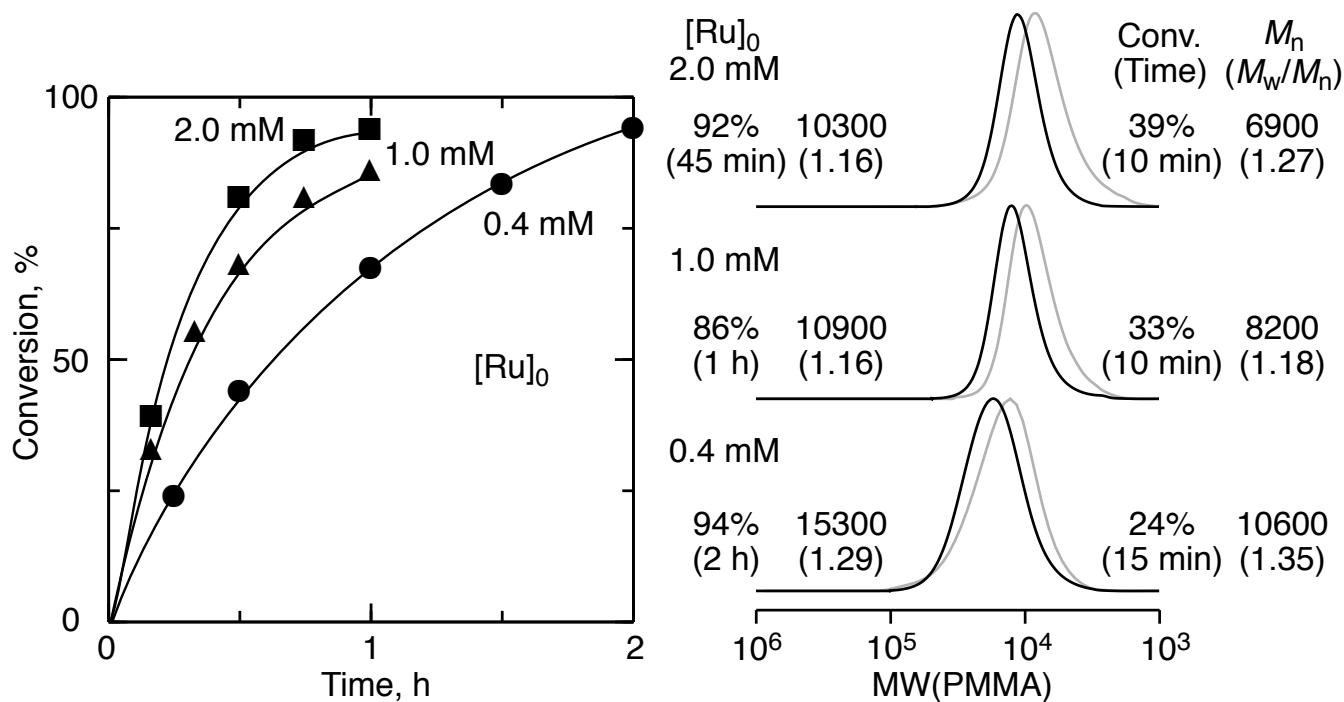


Figure 6

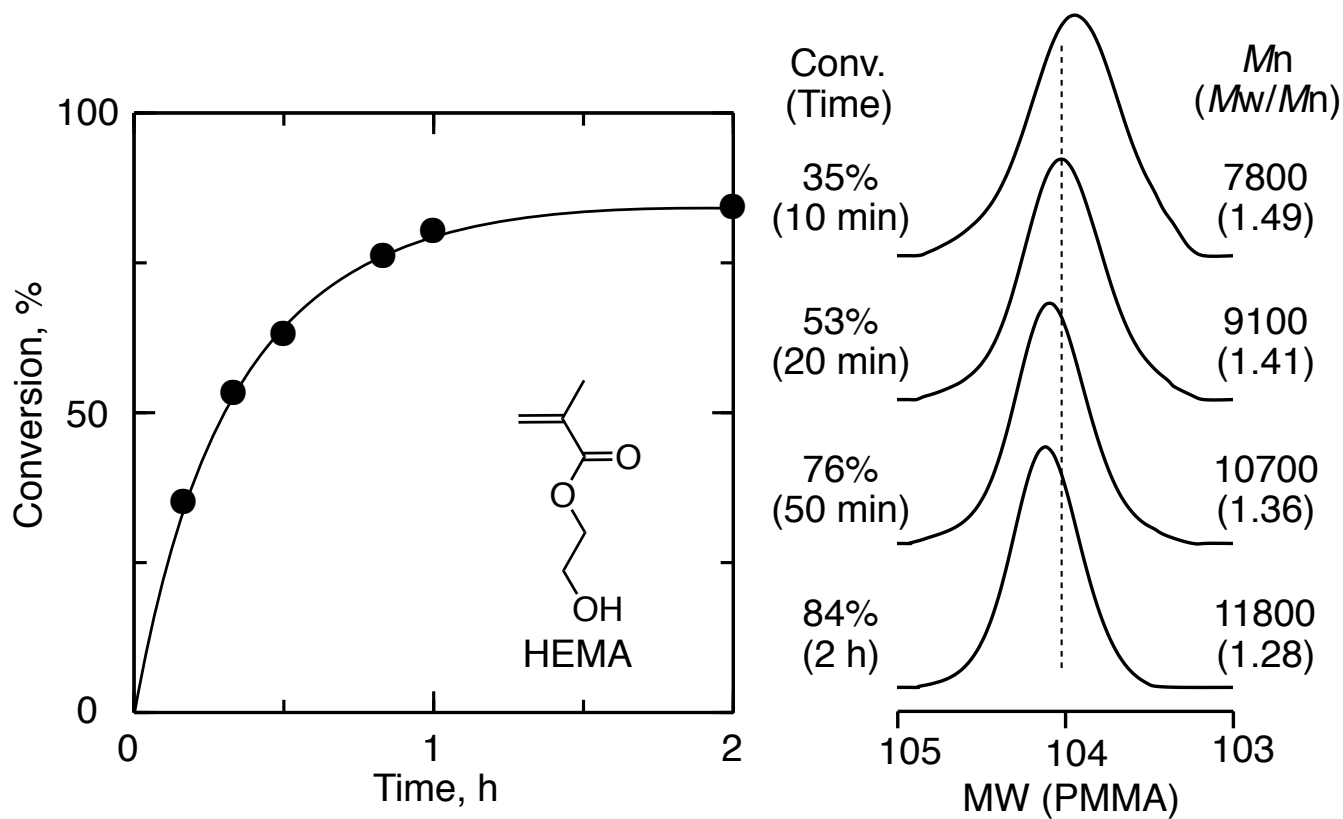


Figure 7



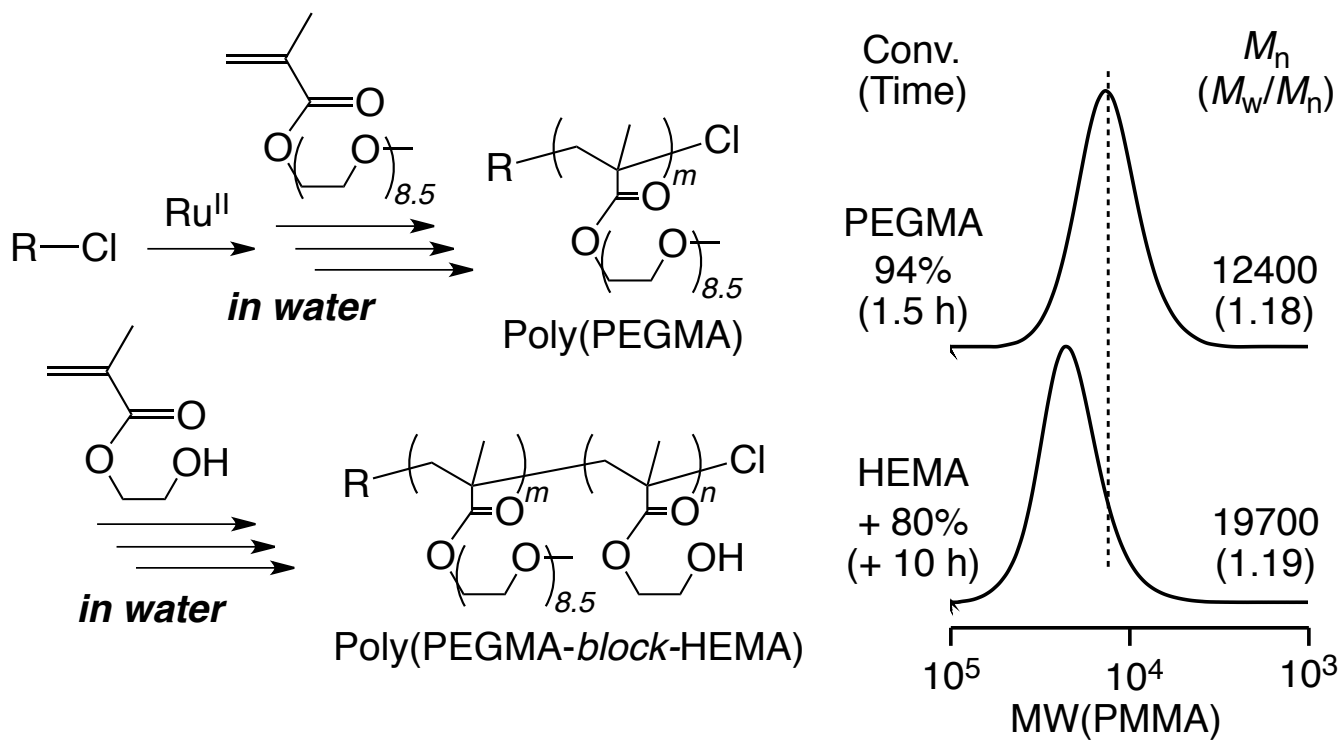
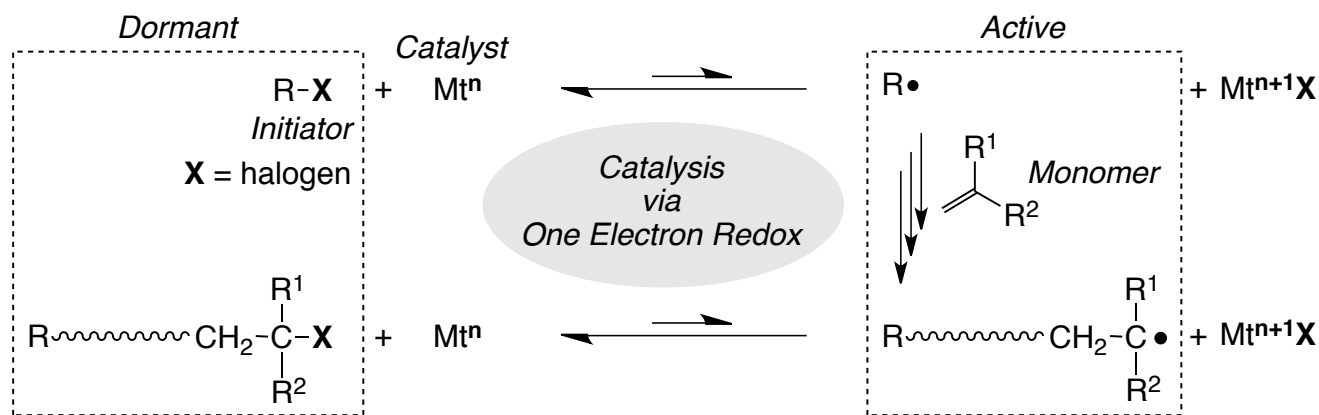
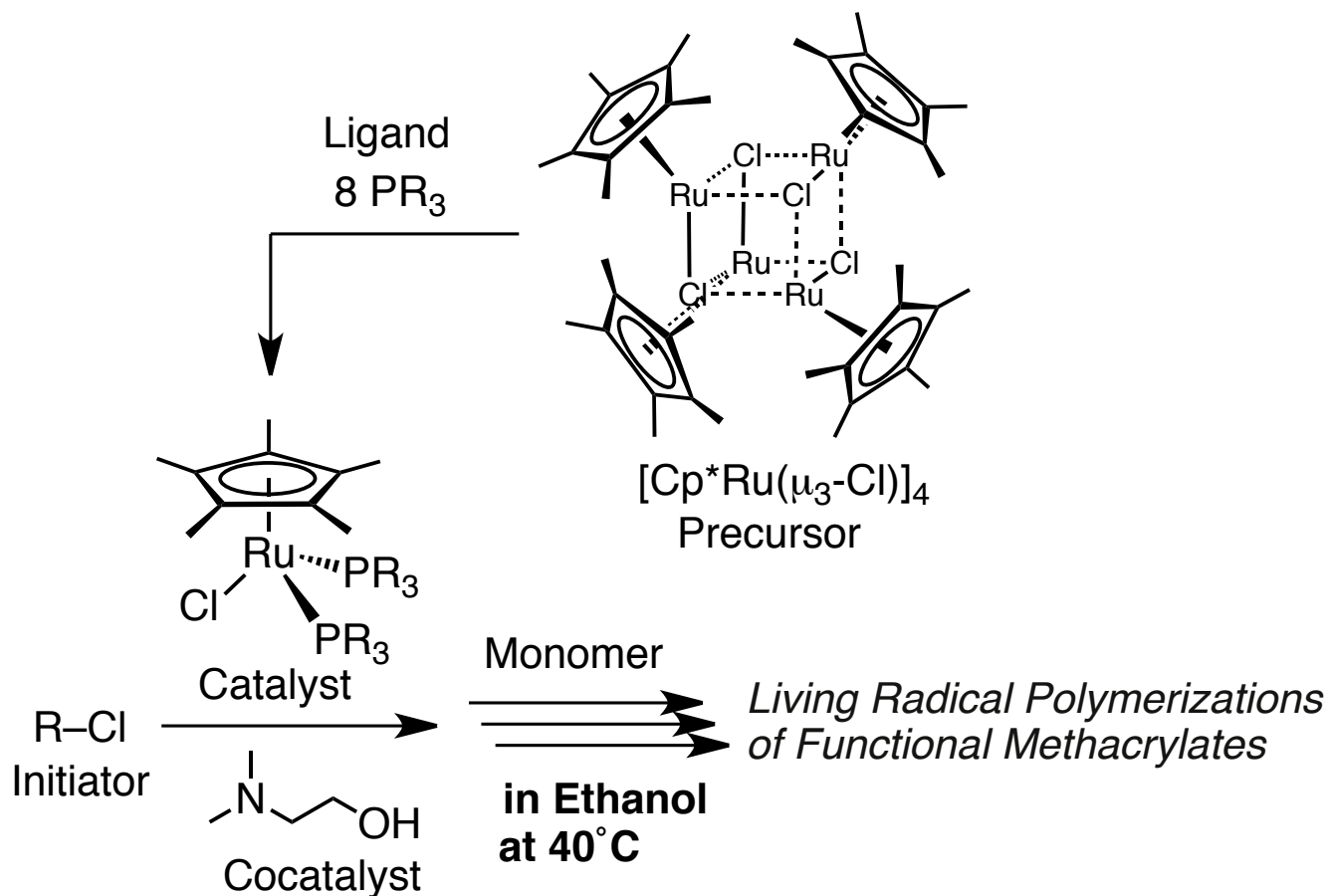


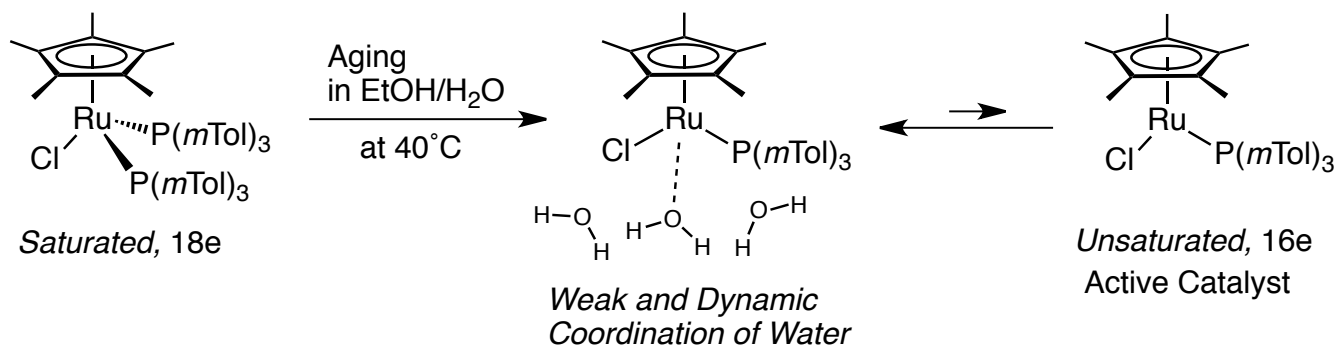
Figure 8



Scheme 1



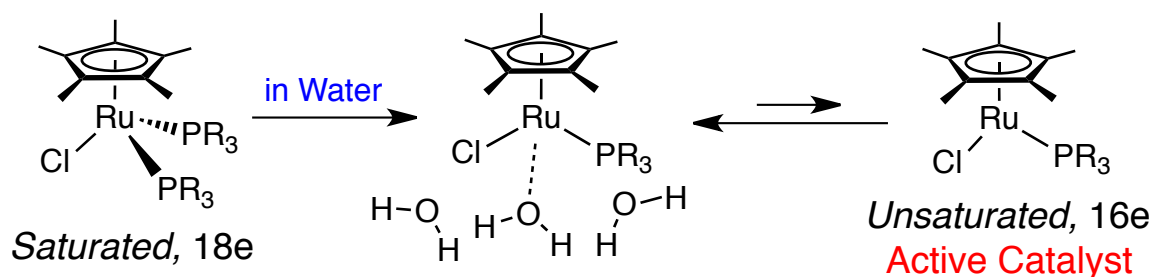
Scheme 2



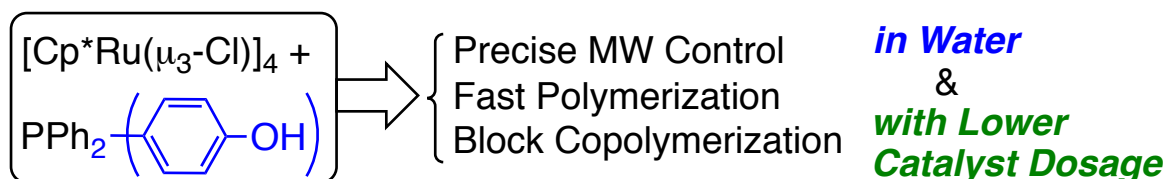
Scheme 3

# Metal-Catalyzed Living Radical Polymerization in WATER

## Water-Assisted Dynamic Transformation into Active Complex



## Highly Active Catalysis in Water with Hydrophilic Ligand



Graphical Abstract